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An Updated Concept for Left Ventricular Hypertrophy Risk in Hypertension

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ABSTRACT

Left ventricular hypertrophy (LVH) was one of the first three ''factors of risk'' originally identified by the Framingham Heart Study predisposing the patient to premature morbidity and mortality resulting from coronary heart disease. Among the initial approaches toward specific risk reduction were antihypertensive agents that reduce left ventricular (LV) mass with control of arterial pressure. However, the indication to reduce risk from LVH has not been approved by the federal regulatory agency. All drugs that reduce arterial pressure are capable of decreasing LV mass. More recently, investigative efforts in the laboratory and clinic have focused on identifying specific epiphenomena that are responsible for risk; they include ischemia, fibrosis, apoptosis, dietary salt excess, and inflammatory factors. Newer clinical methods are becoming available to diagnose these alterations. Current antihypertensive therapy and management improve coronary blood flow and flow reserve, diminish ventricular fibrosis and apoptosis, employ established educational interventions to reduce dietary salt intake, and may prevent inflammatory factors (although the latter factor requires further study; and others, no doubt, will continue to be identified). Thus, present knowledge is available to apply this more current paradigm for the treatment of hypertension and to reduce risk from LVH.

INTRODUCTION

In one of the very early reports from the Framingham Heart Study, the term ''factors of risk'' was introduced to identify those very specific clinical abnormalities that conferred increased risk for premature cardiovascular morbidity and mortality associated with coronary heart disease. Included among those initial cardiovascular risk factors were: hypertension, left ventricular hypertrophy (LVH), and hypercholesterolemia.[1] Since then, additional risk factors have been identified or postulated, but the original three have remained firmly established. However, over the many intervening years, much information has accumulated to suggest that LVH, per se, is not necessarily a specific risk factor. LVH is an adaptive physiological mechanism that can be easily identified clinically and is also associated with a number of pathophysiological epiphenomena that have been tested experimentally and clinically and confer the risk associated with LVH.[2]

The purpose of this report is not to deny the concept that LVH is a ''factor of risk'' but to introduce an updated concept that the myocytic hypertrophy associated with LVH does not necessarily promote increased cardiovascular morbidity and mortality. What is suggested herein is a paradigm for understanding the number of pathophysiological epiphenomena that explain the risk associated with LVH. Hence, they provide enlightened insight into LVH risk. In short, it is not the existence of the hypertrophied ventricular myocytes that actually confers risk, but the inherent risk of LVH is actually produced by a number of associated pathophysiological epiphenomena.

EARLY PATHOPHYSIOLOGICAL CONCEPTS

The earliest clinical reports made a careful distinction between two terms frequently used today in clinical medicine (albeit, perhaps, incorrectly): coronary heart disease and coronary arterial disease. By coronary heart disease the early epidemiologists carefully identified specific clinical endpoints that are associated with the increased morbidity and mortality associated with coronary vascular and ventricular disease related to hypertension and/or occlusive atherosclerotic epicardial coronary arterial disease. Thus, a very real difference exists between epicardial coronary atherosclerotic disease and the cardiovascular and myocardial involvement that constitute hypertensive heart disease (HHD).[3] Endothelial dysfunction also occurs with both diseases as well as with ventricular ischemia and thereby accounts for the diminished coronary blood flow and flow reserve as well as the ventricular involvement from both diseases. Therefore, in HHD there is: left ventricular (LV) myocytic hypertrophy; ischemia of both the left and right ventricles on the basis of endothelial dysfunction

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as well as the coronary arteriolar constriction that is shared by all arterioles of the systemic circulation; increased ventricular wall tension that is explained by the increased systolic pressure and the transverse diameter of the ventricle; and, more recently elucidated, additional epiphenomena associated with the development of the LV myocytic hypertrophy (e.g., fibrosis, apoptosis, chronic dietary salt overloading, inflammatory changes and, no doubt, other mechanisms yet to be elucidated).[2,4]

HEMODYNAMIC ALTERATIONS

Brief discussion is in order concerning the altered systemic hemodynamic and ventricular abnormalities associated with hypertension and LVH. These factors include structural changes such as arterial compression by the hypertrophied ventricle, diminished vascularity of the ventricle and ventricular wall changes in the extracellular matrix of the ventricle and periarteriolar areas.[2]

As already suggested, in HHD a number of functional changes are related to the increased oxygen demand based on the magnitude of the increased ventricular wall tension. Additionally, there is altered autoregulatory reserve and, of course, the impaired coronary hemodynamics associated with the extent of the LVH.[2] Further, a variety of changes are associated with the endothelial dysfunction not only related to impaired endothelial nitric oxide synthesis locally in vascular endothelium and ventricle but also, in part, to the renin-angiotensin-aldosterone (RAAS), kinin, and other humoral mechanisms. In this regard, specific words must be stated relating to the role of the local cardiac RAAS and kinin systems.[5,6] Thus, much recent information has been demonstrated that not only concerns the classical RAAS but also local systems within the heart that involve the arterioles, its extracellular matrix, and the cytoplasm and nuclei. Thus, the angiotensin II, which has been shown to be generated systemically, also participates locally within the ventricle to provide autocrine, pericrine, and even intracrine actions that importantly participate in the local cardiac biological and metabolic effects on cardiac and vascular structural, functional, mitogenic, and other actions.[5–7]

EARLY CLINICAL CORRELATES OF LVH

Soon after Framingham suggested that LVH is a risk factor,[1] we undertook a series of studies designed to identify specific means for clinical cardiac assessment in order to demonstrate progression of HHD.[8–14] In our studies, by definition, all patients having hypertension must have had an elevated arterial pressure (i.e., increased systolic and diastolic pressure equal to or greater than 140 and/or 90 mmHg, respectively). The only diagnostic modalities for LVH at that time were provided by the chest roentgenogram (x-ray) and the 12-lead electrocardiogram (ECG). Using these two techniques, we identified those indices of LVH that provided the best evidence of that structural LV involvement.[8–10] In addition, we also included established ECG criteria of left atrial enlargement or abnormality (LAAb) that were highly concordant with other clinical criteria (e.g., the fourth heart sound or atrial diastolic gallop or the ''bruit-de-gallop'' of Potain).[15] We had already established that those patients having LAAb had higher arterial pressures and an increased prevalence of atrial dysrhythmias.[8] We also provided evidence that those patients we studied with LAAb or LVH who had a history of chest pain demonstrated no structural evidence of occlusive epicardial coronary arterial disease by selective coronary arteriography. However, their intraventricular pressure curves demonstrated a pre-systolic elevation that is compatible with reduced LV distensibility.[10]

We then determined the systemic hemodynamic findings of three groups of patients with hypertension all of whom had significantly elevated arterial pressures and faster heart rates.[10,11,13,14] Group I patients demonstrated no x-ray and/or ECG evidence of LAAb or LVH. All patients in Group II satisfied at least two (of four) ECG criteria of LAAb, which were associated with a reduced LV pre-ejection period and increased total peripheral resistance, but they demonstrated no evidence of LVH. Patients in Group III demonstrated LVH (by ECG), and all patients in that group also demonstrated ECG evidence of LAAb. Additionally, the systemic hemodynamic measurements of the three groups demonstrated a significantly progressive increase in arterial pressure from Groups I to II to III and a faster heart rate in each group (albeit not progressively so). In addition, all patients in Group III (with LVH) demonstrated a significantly reduced resting cardiac index, a diminished LV ejection time and LV ejection rate, and an increased LV stroke work, power, tension time index, and pressure time/beat.[10]

We then adapted the non-invasive technique of 2D, M-mode echocardiography (echo) for the first study reported of patients with HHD.[16] In that study, we employed the identical ECG criteria for three new unstudied groups of patients classified by the same criteria for the earlier study (all had an increased arterial pressure and faster heart rate). None of those patients in Group I had increased LV mass or increased posterior wall or septal ventricular diameters. However, every patient in Groups II and III demonstrated increased LV mass and thicknesses of their posterior and septal wall diameters.[16] Moreover, a decreased LV ejection fraction and fractional fiber shortening rate were demonstrated in all patients of

both Groups II and III although the resting cardiac index was reduced only in those patients of Group III. Thus, at an early stage of HHD, when only LAAb was identified by ECG, we demonstrated significantly impaired LV structural and functional changes characteristic of LVH. Most importantly, the patients in Group II with only LAAb by ECG had echo evidence of LVH even before ECG evidence of LVH was present. Furthermore, all patients in Groups II and III (with ECG and echo evidence of LVH) demonstrated diminished LV structural and functional changes characteristic of LVH.[16] We therefore identified hemodynamic and structural correlates associated with the progression of HHD from no structural changes (Group I) to LAAb (Group II) with early LVH (by echo) to clear-cut LVH (Group III) by ECG and by echo.

PHARMACOLOGICAL REDUCTION IN LV MASS

At this chronological point in our studies of LVH, questions arose concerning potential benefit of therapeutic reduction of LV mass experimentally in the spontaneously hypertensive rat (SHR) or clinically in patients with essential hypertension. Our studies and those of others were designed to demonstrate whether reduced LV mass was beneficial and reduced risk; and every type of pharmacological intervention was shown to reduce LV mass to a greater or lesser extent.[3,17–35] However, methyldopa demonstrated disturbing evidence of increased LV hydroxyproline (collagen) content.[21,22,36] This raised concern that perhaps associated with this means for reducing LV mass, the increased fibrosis may actually predispose the patient to develop cardiac failure (especially if therapy was precipitously discontinued).[37]

Clinical studies similarly demonstrated reduced LV mass, although none presented actual histological evidence of reversed hypertrophy of ventricular myocytes. Nevertheless, some clinical investigators reported that the reduced LV mass also decreased the cardiovascular risk of their patients demonstrating reduced strokes and cardiovascular protection whereas their positive control (which did not reduce LV mass) failed to demonstrate that protection.[38–40] Thus, even if LV mass were reduced, so was the arterial pressure of their patients. Therefore, was it possible that the pressure reduction (per se) may have provided an explanation for the reported reduced risk although those patients receiving a positive control medication also reduced pressure?[39,40] However, to my way of thinking, even if LV mass were reduced, so was the arterial pressure. Hence, it was possible that the pressure reduction, per se, may have provided an explanation for the reported risk reduction even though the positive control medication also reduced pressure. In fairness, the positive pharmacological control agent (atenolol) also reduced pressure significantly, but question has been raised concerning this beta-adrenergic receptor blocking agent.[20,41] This lack of acceptance of the benefit of coincident reduction of risk by decreasing ECG and/or echo evidence of LVH has been supported importantly by the position taken by governmental regulatory agencies in giving approval to this assertion for a clinical indication of that therapy. At this point in the ''LVH risk story,'' a new series of experimental and clinical findings were appearing; and these studies provided a new understanding about the underlying mechanisms to explain the risk associated with LVH. Discussion of this area of related experimental and clinical investigation follows.

MECHANISMS OF THE FACTORS UNDERLYING LVH RISK

At the outset of this discussion, the background of the term ''risk factors'' was introduced and, subsequently, the clinical correlates of the associated clinico-pathophysiological findings of LVH were presented.[1] Since that initial Framingham Heart Study report, new clinical concepts have evolved. Among them are such conditions as ventricular remodeling, diastolic dysfunction with preserved ejection fraction (i.e., normal systolic function), ventricular fibrosis, and apoptosis. These and other alterations clearly impact upon the overall risk of LVH, particularly as they concern the patient with hypertension.

The message to be derived from his report is that LVH should be considered not as a ''risk factor,'' per se, but that it introduces a new concept concerning LVH risk. It introduces a new paradigm that must recognize the underlying mechanisms of LVH and its risk. This thinking is essential for selecting a modern approach for diagnosis and treatment; and to this end, consideration of LVH as a risk factor should not be abandoned. To the contrary, inherent in its recognition the clinician must be acutely aware of those underlying mechanisms that are responsible pathophysiologically for the premature mortality and morbidity attributed to LVH. Newer diagnostic tools are available and will be introduced clinically that will recognize these underlying pathophysiological alterations, and, equally important, specific therapeutic interventions that can be directed toward them. Thus, it is not the enlarged LV in hypertension that is responsible for that risk; it provides the rationale for identifying the fundamental means to recognize the alterations and appropriately manage them rather than the need to reduce the increased ventricular mass, per se. Medicine has now evolved in its knowledge to appreciate this new paradigm that

enhances an enlightened approach for more specific diagnosis, treatment, and management.

Well appreciated by clinicians is that all antihypertensive therapy will diminish ventricular mass to a greater or lesser extent,[2,3] although certain agents may have more specific actions on the underlying mechanisms. The common denominator of presently appreciated therapy has been reduction and control of arterial pressure, LV afterload, and, of course, ventricular tension and workload. Additional goals of therapy should also include normalizing resting myocardial blood flow and flow reserve; recognition, prevention, and reversal of fibrosis; reducing and preventing apoptosis and inflammatory changes; achieving better control of dietary salt intake; and, of course, a continuing and vigorous search for other underlying disease factors. In this regard, future additional enlightened therapeutic approaches may not even be associated, alone or partly, with arterial pressure control. Each of these concepts will be discussed below.

Ischemia

Of the epiphenomena to be discussed, ventricular ischemia is the one that has been appreciated the longest. Even without co-existing atherosclerotic epicardial coronary arterial disease, ischemia related to HHD has been a classical cause of angina pectoris. Experimental and clinical studies have demonstrated that by increasing LV tension (i.e., the product of the increased transverse cardiac diameter and elevated systolic pressure) significant ischemia can produce angina pectoris).[2,3,10,11] Moreover, many experimental and clinical studies have demonstrated impaired LV coronary blood flow and flow reserve in hypertension.[42–46] These studies based on the above described methods have demonstrated reduced coronary flow reserve and minimal coronary vascular resistance. Thus, even if resting coronary blood flow is normal under controlled experimental as well as clinical conditions, coronary flow reserve and minimal coronary vascular resistance has been shown to be abnormal (and may be considerably improved with administration of pharmacological agents that have been demonstrated to be effective in patients with angina.[35,47,48]

Clinical practice of medicine routinely employs established techniques for determination of coronary flow reserve. This has been assessed clinically by well-established exercise stress testing. In addition, greater sophistication for assessment of coronary flow reserve has employed pharmacological interventions that permit more precise quantification. Indeed, these interventions have included such agents as carbochrome, papaverine, dipyridimole, and adenosine. Some have been used clinically with radioisotopic techniques to quantify or provide concepts of myocardial perfusion and impaired coronary flow. Our experimental studies with the SHR rat have demonstrated increased coronary flow and flow reserve, reduced coronary vascular and minimal coronary resistance, and the effects of the broad spectrum of antihypertensive agents.[17–32,47–49] These findings have been supported by a long clinical experience of the extreme usefulness of these agents in patients with hypertensive and atherosclerotic coronary vascular and heart disease.

Clearly, many questions exist concerning relevant clinical issues that must be resolved related not only to hypertensive but also to atherosclerotic ischemic coronary vascular disease. One such problem is why such agents as the calcium antagonists are extremely useful not only in increasing coronary blood flow and reducing coronary vascular resistance but also in producing remission of chest pain associated with myocardial ischemia. On the other hand, the angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) that have similar coronary hemodynamic effects are not useful for remitting angina pectoris.

Endothelial Dysfunction and Arteriolar Constriction

Endothelial dysfunction is a broadly used term that has been used experimentally and clinically to provide one explanation for diminished ventricular and/or vascular blood flow to other body tissues that results from impaired endothelial generation of nitric oxide from the natural amino acid L-arginine.[50,51] This endothelial derangement occurs in a number of conditions, including hypertension, atherosclerosis, diabetes mellitus, obesity, aging, menopause, smoking, and others. The result of this abnormal mechanism in HHD and/or atherosclerotic cardiovascular disease provides yet another means for the coronary vessels and ventricles to develop ischemia and endothelial dysfunction. The net local effect of this metabolic defect is the generation of reactive oxygen species and oxidative stress, which result from abnormal nitric oxide synthesis in the endothelium from one or more of the multifactorial causes of ischemia in hypertensive cardiovascular disease. Because of the complexity and multiple biological changes thereby induced, the reader is referred to several recent key reports, discussions, and reviews dealing with this subject.[49–60] However, it is reasonable to conclude that this relatively new mechanism explains, at least in part, the ischemia in hypertensive cardiac and vascular disease. Thus, the ischemia resulting from this endothelial alteration (i.e.,''dysfunction'') participates over and above that from the vasoconstriction and ischemia produced by the generalized arteriolar disease that occurs in all

organs, thereby explaining (in great part) much of the major target organ functional impairment of the target organs of hypertensive cardiac, vascular, and renal diseases.[50,51]

Fibrosis

Ventricular fibrosis has not been generally considered a mechanism of risk until relatively recently. The development of fibrosis accounts importantly for the impaired ventricular contractile function and the cardiac failure in patients with LVH with HHD and/or atherosclerotic coronary arterial disease. Indeed, it has been considered to be of tremendous importance and significance for many years, but its role in explaining the risk of LVH has been broadly acknowledged.[61–70]

Along this line of thinking, the concept of ventricular fibrosis and remodeling has been well known for over a decade.[71–73] Thus, the concept of prevention of ventricular remodeling with ACE inhibitor therapy was demonstrated coincident with immediate treatment following myocardial infarction. This finding was so dramatic that ACE inhibitor therapy was also shown to prevent cardiac failure, a second myocardial infarction, and death following myocardial infarction.[71–73] Since this initial report, a number of confirmatory double-blind, placebo-controlled multicenter trials were reported using other ACE inhibitors.[74] In addition, the negative effects of this adverse response of ventricular remodeling following myocardial infarction were reported experimentally and clinically in a series of studies demonstrating prevention of ventricular remodeling, cardiac failure, and death by an ACE inhibitor.[73]

With respect to the role of ventricular fibrosis with LVH experimentally and clinically in patients with essential hypertension, a number of reports have demonstrated the appearance of collagen (i.e., fibrosis) with its subsequent reversal using agents that inhibit the action of angiotensin II on myocytic, fibromyocytic, extracellular ventricular matrix, and perivascular arteriolar components with the deposition of collagen experimentally and clinically. Thus, these negative effects of this adverse response to myocardial infarction were reported experimentally and clinically in a series of studies demonstrating the prevention of ventricular remodeling, cardiac failure, and death following myocardial infarction by ACE inhibitors.[34,74–79]

These events with development of ventricular fibrosis occur not only following the foregoing expressions of ischemic heart disease from atherosclerosis but, importantly, with experimentally and clinically associated ischemia associated with HHD. Furthermore, the fibrosis thus developed involves not only the hypertrophied left ventricle but, also, the non-hypertrophied right ventricle and the interventricular septum with hypertension and with aging.[75]

A number of experimental studies in our laboratory have demonstrated dramatic reversal of ventricular fibrosis with treatment using antihypertensive agents that inhibit the RAAS.[27,29–31,33–35,49,61–70] We have shown that the ACE inhibitor and ARB are effective when used alone and exacerbated each other in increasing coronary blood flow when these agents were used together; but, unfortunately, collagen was not measured in that study.[33] The postulated mechanism offered for this latter action is not only the ability of the ACE inhibitor to reduce generation of angiotensin II and the antagonistic action of angiotensin II that escaped conversion by the ACE inhibitor but also the action of the enzyme chymase, which is found in greater abundance in the rat ventricle (and even more the human ventricle) to exert its hemodynamic and mitogenic actions.

Before concluding this discussion on fibrosis, it is important to refer to the remarkable dynamic status of fibrosis and its responsiveness to pharmacological interventions that serves to prevent or reverse this fibrosis clinically. Several prospective clinical studies have demonstrated the dramatic response of the ventricles to reverse fibrosis by agents that inhibit the RAAS. These independent investigators significantly prevented and reversed the fibrosis with these agents but not with the thiazide diuretic.[77–79] These findings were confirmed by ventricular biopsy studies in these patients without any evidence of atherosclerotic epicardial coronary arterial disease.

Of particular pertinence has been the demonstration of increased circulating levels of pre-procollagen in the blood of patients with LVH, which has been correlated directly and significantly with the collagen concentration in the ventricle before and after the pharmacological reduction of LV mass.[64,65] Other biological markers presently under study no doubt will provide much insight into the mechanisms involved in the production and reversal of LVH in hypertension; however, the details of these studies are not in the purview of this overall discussion.

As discussed below, dietary salt-loading experimentally has also been shown to promote a most remarkable increase in ventricular fibrosis, discussed above in the SHR and in patients with essential hypertension. Most interestingly, treatment with ARBs (contemporaneously with the salt-loading) dramatically prevented development of fibrosis. These findings are most intriguing and will be discussed in detail below.

Apoptosis

Another pathophysiological mechanism that imparts significant cardiovascular risk for premature cardiovascular morbidity and mortality is apoptosis. By apoptosis we refer to actively programmed cellular

death by biological mechanisms (e.g., angiotensin II). By contrast, this mechanism acts in striking contrast to the sudden cellular death such as that which results following obliteration of an arterial supply to an organ or tissue (e.g., myocardial infarction, stroke, or embolic disease to a kidney or a peripheral artery). Thus, apoptosis occurs as a progressive disappearance of functioning cardiac myocytes leading to reduction of normally functional ventricular muscle mass.[80] Angiotensin II is one naturally occurring agent that may promote apoptosis; a number of studies have demonstrated this phenomenon.[81,82]

For years we have known that hypertension has been the most common cause of cardiac failure.[83,84] The logical explanation for the earlier findings of cardiac failure is that of impaired systolic ventricular function, most likely explainable on the basis of either no or ineffective antihypertensive therapy.[83] On the other hand, the most frequent causes of cardiac failure today are the progressive (and repeated) episodes of diastolic functional capacity of the heart with preserved systolic function.[84,85] This latter form of impaired ventricular function is the most common cause (at present) of hospitalization in elderly patients in industrial societies.

In one recent report of apoptosis in patients with essential hypertension, apoptosis of cardiac myocytes as well as non-myocytes was more common in these patients than in normotensive subjects.[81,86] Furthermore, when two groups of hypertensive patients were treated with either an ARB or a calcium antagonist, there was a highly significant decrease in apoptotic cells with ARB treatment; however, in contrast, there was a failure of the calcium antagonist to reduce the apoptotic cells.[86] Although this extremely fascinating expression of translational research is compelling, further studies along this line of research are clearly necessary. The major points raised by these exciting findings are that they provide further evidence that the same humoral agents shown to be responsible for the development and reversal of fibrosis have also been shown to be responsible for promoting and reversing the risk associated with apoptosis. Further reports of further clinical and experimental investigative work are eagerly anticipated.

Dietary Sodium Excess

Two major areas of continued clinical concern with respect to management of hypertensive disease include the persistent rise in the prevalence of cardiac failure and end-stage renal disease from the advent of effective antihypertensive therapy.[87] These issues are in striking contrast to the dramatically decreasing prevalence of deaths resulting from stroke and from coronary heart disease since the advent of effective antihypertensive therapy. Moreover, over these years (since the advent of antihypertensive therapy), there has been no postulated explanation for the impressive and highly significant relationship between the prevalence of hypertensive disease in societies and the effects of chronic salt loads.

This relationship is particularly perplexing especially since the minority of patients with essential hypertension do not demonstrate an increased arterial pressure with acute salt-loading (i.e., salt-sensitivity). Although a cause/effect relationship for the sequence of pathophysiological events relating salt excess and hypertension has not been provided, we have postulated a possible explanation for these data.[88] We have suggested that one must take into consideration not necessarily the immediate response of arterial pressure to salt-loading but rather the long-term effects of dietary salt excess on the target organs of hypertensive disease. For many years, studies from our laboratory have involved healthy, adult, male SHR rats having normal cardiac and renal function that were given chronic dietary salt excess. These studies were conducted to determine the structural and functional consequences of prolonged dietary salt-loading to the structural and functional consequences of the target organs of hypertensive disease.[89–100]

In our efforts, one group of SHRs was given a salt-surfeit (8%) daily diet whereas their SHR litter-mate rats that also naturally develop hypertension as well as normotensive Wistar-Kyoto control rats received an otherwise normal salt diet. Each of these studies was conducted similarly to determine whether the salt-loading diet produced significant impairment in cardiac, vascular, and renal structure and function. These studies specifically addressed the responses of the heart, vessels, and kidneys after 12 weeks of salt-loading on various manifestations of abnormal cardiac structure and function.

Our findings dramatically demonstrated severely impaired LV diastolic functional indices associated with further increase in left and right ventricular mass, diminished left and right ventricular coronary blood flow and flow reserve, and increased hydroxyproline concentration (an index of collagen) in both the left and right ventricles with histological demonstration of biventricular fibrosis associated with increased extracellular and perivascular fibrosis.[92,93,100] Similar findings involving the ascending aorta demonstrated impaired vascular distensibility and increased pulse wave velocity.[92,95,97–100]

Further, following prolonged feeding of increasing amounts of salt-loaded diets (4%, 6%, or 8%) given to similar groups of SHRs and their controls, markedly impaired renal structure and function were demonstrated.[92,95–100] As a result, total renal flow, glomer-

ular filtration rate, and filtration fraction were markedly diminished associated with massive proteinuria and markedly increased serum creatinine and uric acid concentrations.[92] Further, renal micropuncture studies demonstrated decreased single nephron plasma flow and increased afferent and efferent glomerular arteriolar resistances associated with increased glomerular hydrostatic pressures.[96] Of great interest, each of these impaired cardiac, vascular, and renal structural and functional changes were markedly prevented when either of two different ARBs were given along with the salt-loading.[100] Thus, these pathophysiological changes induced by salt-loading were remarkably similar and analogous to the changes seen in essential hypertensive patients.[88]

Similar experimental studies have been reported in other models of hypertension; a number of studies involving salt-loading have been reported dealing with patients with essential hypertension.[88] Most notably was a prospective multicenter trial involving two groups of prehypertensive patients: One received a diet restricted in salt, whereas the other consumed their usually salt-loaded diet. In this first well-controlled study of the kind, the cardiovascular morbidity and mortality of the salt-restricted group were significantly less than those of the salt-loaded group.[101] A number of recent clinical studies using a variety of agents that interfere with the cardiac, vascular, and renal effects of angiotensin II have also demonstrated either prevention or improvement of their respective structure and function.

The data demonstrated that the salt-restricted diet dramatically and significantly reduced the primary endpoints responsible for cardiovascular morbidity and mortality. Hence, there is recent clinical evidence demonstrating that cardiovascular risk can be prevented dramatically by intervening with inhibition of yet another means for promoting increased morbidity and mortality, and we therefore suggest that dietary salt excess is another cardiovascular risk factor.

Inflammatory Changes

Still more recently, yet another area of study has focused on the role of inflammation related to cardiovascular morbidity and mortality. In one early study, systolic and diastolic pressure elevation was noted in male and female individuals who were monitored with measurements of plasma C-reactive protein levels.[102] These findings demonstrated that as the systolic or diastolic pressures rose, so did the plasma levels of C-reactive protein and cardiac morbidity and mortality. Further, at a recent meeting of the American College of Cardiology, current investigative work was presented (but with yet to be refereed or published data) that further stimulates thinking about the role of inflammation in promoting events secondary to hypertensive heart disease. Clearly, further data are anticipated; but, who knows what mechanisms may next arise?

CONCLUSIONS

LVH is one of the first three ''factors of risk'' postulated to predispose a patient to premature cardiovascular morbidity and mortality from coronary heart disease. Over the years, the clinical approach for the hypertensive patient with LVH was to prescribe antihypertensive agents that were more likely to reduce LV mass, although that indication was never approved by the federal regulatory agency. However, we know that all drugs that lower arterial pressure will reduce LV to greater or less amounts without proportional reduction of risk. Recent laboratory and clinical studies have been directed to determine those underlying mechanisms that explain the risk associated with LVH. Among these risk epiphenomena that are associated with the development of LVH are ischemia, fibrosis, apoptosis, long-standing dietary salt excess, and inflammatory factors. Today, appropriate antihypertensive therapy is available that will improve coronary arterial blood flow and flow reserve, reduce ventricular fibrosis and apoptosis, and reduce dietary salt loading through appropriate education measures; early research efforts are underway to prevent inflammatory factors (although the latter risk factor and, presumably other factors must yet be identified). Newer diagnostic modalities are under investigation to add to improved management for the patient with hypertension having LVH. Hence, after more than 50 years, knowledge is becoming available to explain the risk associated with LVH and to direct clinical management to reduce its associated risk.

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